WHAT IS CLAIMED IS:

1. A process comprising:

(i) contacting a Target Biological Molecule (TBM) having a first and a second site of interest, and containing or modified to contain a nucleophile at or near the first site of interest with a plurality of first small organic ligand candidates, said candidates having a functional group reactive with the nucleophile, under conditions such that a reversible covalent bond is formed between the nucleophile and a candidate that has affinity for the first site of interest, to form a TBM-first ligand complex;

(ii) identifying the first ligand from the complex of (i); and

(iii) designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest.

2. The process of claim 1 wherein said TBM is contacted with said ligand candidates sequentially.

3. The process of claim 1 wherein said first ligand candidates are members of a library.

4. The process of claim 1 wherein said TBM is a polypeptide.

5. The process of claim 4 wherein said TBM is a protein.

6. The process of claim 5 wherein said protein is selected from the group consisting of lymphocyte cell surface receptors, enzymes, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors, serine/threonine kinases and dephosphorylases, threonine kinases and dephosphorylases, bacterial enzymes, fungal enzymes and viral enzymes, signal transduction molecules, transcription factors, proteins associated with DNA and/or RNA synthesis or degradation, immunoglobulins, hormones, cytokine receptors, chemokines and their receptors, ligands and receptors for tyrosine kinase, neurotrophins and their ligands, and other hormones and receptors.

7. The process of claim 6 wherein said protein is selected from the group consisting of erythropoietin (EPO), granulocyte colony stimulating (G-CSF) receptor, granulocyte macrophage colony stimulating (GM-CSF) receptor, thrombopoietin (TPO), interleukins, e.g.

IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-11, IL-12, growth hormone, prolactin, human placental lactogen (LPL), CNTF, oncostatin, RANTES MIPβ, IL-8, insulin, insulin-like growth factor 1 (IGF-1), epidermal growth factor (RGF), heregulin-α and heregulin-β, vascular endothelial growth factor (VEGF), placental growth factor (PLGF), tissue growth factors (TGF-α and TGF-β), nerve growth factor (NGF), bone morphogenic factors, follicle stimulating hormone (FSH), luteinizing hormone (LH), tissue necrosis factor (TNF), apoptosis factor-1 and –2 (AP-1 and AP-2), and mdm2.

8. The process of claim 6 wherein said protein is selected from the group consisting of IgE/IgER, ZAP-70, lck, syk, ITK/BTK, TACE, Cathepsin S and F, CD11a, LFA/ICAM, VLA-4, CD28/B7, CTLA4, TNF alpha and beta, (and the p55 and p75 TNF receptors), CD40L, p38 map kinase, IL-2, IL-4, Il-13, IL-15, Rac 2, PKC theta, IL-8, TAK-1, jnk, IKK2 , IL-18, caspases 1, 3, 8 and 9, IL-1/IL-1 receptor, BACE, HIV integrase, PDE IV, Hepatitis C helicase, Hepatitis C protease, rhinovirus protease, tryptase, cPLA (cytosolic Phospholipase A2), CDK4, c-jun kinase, adaptors such as Grb2, GSK-3, AKT, MEKK-1, PAK-1, raf, TRAF's 1-6, Tie2, ErbB 1 and 2, FGF, PDGF, PARP, CD2, C5a receptor, CD4, CD26, CD3, TGF-alpha, NF-kB, IKK beta, STAT 6, Neurokinin-1, PTP-1B, CD45, Cdc25A, SHIP-2, TC-PTP, PTP-alpha, LAR and human p53, bax/bcl2 and mdm2.

9. The process of claim 1 wherein said nucleophile is selected from the group consisting of thiol, protected thiol, reversible disulfide, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl and protected carboxyl groups.

10. The process of claim 4 wherein said nucleophile is selected from the group consisting of thiol, protected thiol, reversible disulfide, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl and protected carboxyl groups.

11. The process of claim 10 wherein said nucleophile is associated with a wild-type or mutant Cys, Ser, Thr, Lys, Asp, or Glu present on the TBM.

12. The process of claim 4 wherein said nucleophile is thiol, protected thiol, or a reversible disulfide group.

13. The process of claim 12 wherein said nucleophile is associated with a wild-type or mutant Cys on the TBM.

14. The process of claim 12 wherein said ligand candidates have a thiol, protected thiol or reversible disulfide group.

15. The process of claim 14 wherein step (i) is performed under conditions of thiol exchange.

16. The process of claim 15 wherein said conditions are provided by a reducing agent selected from the group consisting of mercaptoethanol, dithiothreitol (DTT), dithioerythreitol (DTE), mercaptopropanoic acid, glutathione, cysteamine, cysteine, tri(carboxyethyl)phosphine (TCEP), and tris(cyanoethyl)phosphine.

17. The process of claim 9 wherein the first functional group on said SME of step (iii) is capable of forming an irreversible covalent group with the thiol, protected thiol, reversible disulfide bond, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl or protected carboxyl on said TBM.

18. The process of claim 17 wherein said first functional group is capable of undergoing an SN2-like addition or form a Michael-type adduct with the thiol, protected thiol, reversible disulfide, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl or protected carboxyl on said TBM.

19. The process of claim 18 wherein said first functional group is selected from the group consisting of α-halo-acid, fluorophos(phon)ate, epoxide, aziridine, thiirane, halo-methyl-ketone, halo-methyl-amide groups, groups derived from electrophilic aromatic systems, aldehyde, boronic acids, and groups capable of forming Michael adducts with the nucleophile on said TBM.

20. The process of claim 17 further comprising the steps of (iv) contacting the SME with the TBM to form a TBM-SME complex, and (v) contacting the TBM-SME complex with a plurality of second small organic ligand candidates, said candidates having a functional group reactive with the SME in said TBM-SME complex, wherein a candidate that has affinity for said second site of interest on said TBM forms a reversible covalent bond with said TBM-SME complex, whereby a second ligand is identified.

21. The process of claim 20 wherein the second functional group on said TBM and the functional group on said second ligand candidates in step (v) is a thiol, protected thiol or reversible disulfide group.

22. The process of claim 21 wherein step (v) is conducted under conditions of thiol exchange.

23. The process of claim 22 wherein said conditions are provided by a reducing agent selected from the group consisting of mercaptoethanol, dithiothreitol (DTT), dithioerythreitol (DTE), mercaptopropanoic acid, glutathione, cysteamine, cysteine, tri(carboxyethyl)phosphine (TCEP), and tris(cyanoethyl)phosphine.

24. The process of claim 23 wherein said second ligand candidates in step (v) are members of a library.

25. The process of claim 24 wherein the library member having the highest affinity for said second site of interest on the TBM forms a disulfide bond with the TBM-SME complex.

26. The process of claim 9 wherein the first functional group on said SME of step (iii) is capable of forming a reversible covalent group with the thiol, protected thiol, reversible disulfide bond, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl or protected carboxyl on said TBM.

27. The process of claim 26 wherein the nucleophile of the TBM is a thiol, or protected thiol group.

28. The process of claim 27 further comprising the step of (iv') contacting said SME with the TBM to form a TBM-SME complex, and (v') contacting the TBM and SME with a plurality of second small organic ligand candidates, said candidates having a functional group reactive with the SME, wherein step (iv') precedes step (v'), or steps (iv') and (v') are performed simultaneously, and wherein a candidate that has affinity for said second site of interest on said TBM forms a reversible covalent bond with the TBM-SME complex, whereby a second ligand is identified.

29. The process of claim 28 wherein the second functional group on said TBM and the functional group on said second ligand candidates in step (v') is a thiol, protected thiol or reversible disulfide group.

30. The process of claim 29 wherein step (v') is conducted under conditions of thiol exchange.

31. The process of claim 30 wherein said conditions are provided by a reducing agent selected from the group consisting of mercaptoethanol, dithiothreitol (DTT), dithioerythreitol (DTE), mercaptopropanoic acid, glutathione, cysteamine, cysteine, tri(carboxyethyl)phosphine (TCEP), and tris(cyanoethyl)phosphine.

32. The process of claim 31 wherein said second ligand candidates in step (v) are members of a library.

33. The method of claim 20 comprising identifying said second ligand having affinity for said second site of interest on the TBM.

34. The method of claim 33 wherein said second ligand is identified by mass spectrometry (MS).

35. The method of claim 33 wherein said second ligand is identified by means of a detectable tag.

36. The method of claim 28 comprising identifying said second ligand having affinity for said second site of interest on the TBM.

37. The method of claim 36 wherein said second ligand is identified by mass spectrometry (MS).

38. The method of claim 36 wherein said second ligand is identified by means of a detectable tag.

39. The method of claim 33 or claim 36, further comprising the step of synthesizing a molecule comprising said first and second ligands covalently linked to one another.

40. The method of claim 39 wherein said covalent linkage is provided by a disulfide bond.

41. The method of claim 40 wherein said molecule consists essentially of said first and second ligands, covalently linked through a disulfide bond.

42. The method of claim 41 further comprising the step of synthesizing derivatives of said molecule.

43. The method of claim 42 wherein the disulfide bond is replaced with a different covalent linkage.

44. A molecule comprising a second ligand identified in claim 33 or claim 36.

45. The molecule of claim 44 further comprising the first ligand identified in claim 1.

46. The molecule of claim 45 wherein said first and second ligands are linked by a covalent bond.

47. The molecule of claim 46 wherein said covalent bond is other than a disulfide bond.

48. A molecule comprising functional variants of said first and second ligands linked by a covalent bond.

49. The molecule of claim 48 wherein said bond is other than a disulfide bond.

50. A process comprising:

(i) providing a Target Biological Molecule (TBM) containing or modified to contain a reactive nucleophile near a first site of interest on the TBM;

(ii) contacting the TBM from (i) with a small molecule extender having a group reactive with the nucleophile on the TBM and having a free thiol or protected thiol;

(iii) adjusting the conditions to cause a covalent bond to be formed between the nucleophile on the TBM and the group on the small molecule extender thereby forming a covalent complex comprising the TBM and the small molecule extender, the complex displaying a free thiol or protected thiol near a second site of interest on the TBM;

(iv) contacting the complex from (iii) with a library of small organic molecules, each molecule having a free thiol or exchangeable disulfide linking group, under conditions of thiol exchange wherein the library member having the highest affinity for the second site of interest on the TBM forms a disulfide bond with the complex; and

(v) identifying the library member from (iv).

51. The process of claim 50 further comprising the step of synthesizing a molecule consisting essentially of the small molecule extender having the eletrophile group from step (ii) covalently linked through the disulfide with the library member identified in step (i).

52. The process of claim 51 further comprising the step of synthesizing derivatives of the molecule.

53. The process of claim 52 wherein the derivative contains a different group reactive with the nucleophile.

54. The process of claim 52 wherein the disulfide group is replaced with a different group.

55. The process of claim 50 further comprising synthesizing a molecule consisting essentially of the small molecule extender without the group reactive with the nucleophile covalently linked through the disulfide with the library member identified in step (e).

56. The process of claim 55 further comprising replacing the disulfide with a different group.

57. The process of claim 50 wherein the reactive nucleophile is a thiol.

58. The process of claim 57 further comprising, after step (i),

(a) contacting the TBM with a library of small organic molecules, each molecule having an exchangeable disulfide linking group, under conditions of thiol exchange wherein the library member having the highest affinity for the first site of interest forms a disulfide bond with the TBM;

(b) identifying the library member from (i); and

(c) forming a derivative of the library member in (ii) that is the small molecule extender having a group reactive with the nucleophile and having a thiol or protected thiol of step (b).

59. The process of claim 58 further comprising adding a disulfide reducing agent selected from the group consisting of mercaptoethanol, dithiothreitol (DTT), dithioerythreitol (DTE), mercaptopropanoic acid, glutathione, cysteamine, cysteine, tris(carboxyethyl)phophine (TCEP), and tris(cyanoethyl)phosphine.

60. The process of claim 50 wherein the reactive nucleophile is a hydroxyl (-OH) group.

61. The process of claim 60 wherein the group reactive with the nucleophile is selected from the group consisting of an activated carbonyl, epoxide, aziridine, aromatic sulfonate, hemiacetal, halomethylketone, arylacyloxymethylketone, disulfide, thiosulfonate, and thiosulfate.

62. The process of claim 61 wherein said carbonyl is in the form of an aldehyde or ketone or an ester or acyl halide.

63. The process of claim 50 wherein the reactive nucleophile is an amine.

64. The process of claim 50 wherein the identifying step comprises mass spectrum analysis.

65. The process of claim 58 wherein the identifying step comprises mass spectrum analysis.

66. The process of claim 58 wherein the conditions comprising adding a disulfide reducing agent.

67. The process of claim 58 wherein each molecule in the library of small organic molecules having an exchangeable disulfide linking group contains the cysteamine moiety.

68. The process of claim 61 wherein the activated carbonyl is selected from the group consisting of halomethylketones, arylacyloxomethylketones and thioesters.

69. A molecule comprising a library member identified in step (v) of claim 50.

70. The molecule of claim 69 further comprising at least part of the small molecule extender used in step (ii) of claim 50.

71. The molecule of claim 70 comprising said library member and said small molecule extender or part thereof, linked by a covalent bond.

72. The molecule of claim 71 wherein said covalent bond is other than a disulfide bond.

73. A molecule of claim 70 comprising functional variants of said library member and small molecule extender or part thereof, linked by a covalent bond.

74. The molecule of claim 73 wherein said covalent bond is other than a disulfide bond.